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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,458	FEDER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,9 and 16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 04 February 2004 has been entered in full. Claims 1, 8, and 16 are amended. Claims 5-7, 10-15, and 20-34 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 8-9, and 16-19 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2 of the previous Office Action (10 September 2003) are *withdrawn in part* in view of the amended abstract and specification (04 February 2004). See Specification, below.

2. The rejection of claims 1-4, 8-9, and 16-19 under 35 U.S.C. § 112, first paragraph (deposit rules) at pg 13-14 of the previous Office Action (10 September 2003) is *withdrawn* in view of Applicant's submission of a statement by an attorney of record (04 February 2004).

3. The rejection of claims 1-4, 8-9, and 16-19 under 35 U.S.C. § 112, second paragraph as set forth at pg 15 of the previous Office Action (10 September 2003) is *withdrawn in part* in view of the amended claims (04 February 2004). See 35 U.S.C. § 112, second paragraph, below.

Specification

4. The disclosure is objected to because of the following informalities:

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See for example, pg 229, line 21). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP §

608.01. The basis for this objection is set forth at pg 2 of the previous Office Action (10 September 2003).

Although Applicant indicates that the specification has been amended to remove all hyperlinks and other forms of browser-executable code, the amendment incorrectly identifies the page in the specification that needs correction. Therefore, this amendment was not entered. The appropriate page number should be pg 229 rather than pg 239. Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 U.S.C. § 112, first paragraph

6. Claims 1-4, 8-9, and 16-19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth at pg 3-7 of the previous Office Action (10 September 2003).

Specifically, the claims are directed to an isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95.0% or 100% identical to a sequence selected from the group consisting of: (a) a polynucleotide fragment of SEQ ID NO: 1 or a polynucleotide fragment of the cDNA sequence of ATCC Deposit No: PTA-4055, (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO: 2, (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO: 2, (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO: 2, (e) a polynucleotide encoding a polypeptide of SEQ ID NO: 2 or the cDNA sequence of ATCC Deposit No: PTA-4055, which is hybridizable to SEQ ID NO: 1, having potassium channel beta subunit activity, (f) a polynucleotide which is a variant of SEQ ID

NO: 1, (g) a polynucleotide which is an allelic variant of SEQ ID NO: 1, (h) an isolated polynucleotide comprising nucleotides 420-1097 of SEQ ID NO: 1, (i) an isolated polynucleotide comprising nucleotides 417-1097 of SEQ ID NO: 1, (j) a polynucleotide which is the complimentary sequence of SEQ ID NO: 1, (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j). The claims also recite a recombinant vector comprising the isolated nucleic acid molecule, a recombinant host cell, and a method of making an isolated polypeptide.

Applicant's arguments (04 February 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant argues that the homology data provided in the specification supports the assertion that the claimed sequences are potassium channel beta subunits. Applicant states that the specification reports homology at the nucleotide and amino acid level between the claimed sequences and the human Maxi-K potassium channel beta subunit, KCNMB1, the human membrane channel protein-2, the *Drosophila* CG10465, and the *Drosophila* CG10440 protein. Applicant directs the Examiner to Figures 2 and 4, wherein details regarding the homology between the sequences is presented. Applicant indicates that all asserted utilities are specific, substantial, and credible, thereby meeting the statutory requirement of utility.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the assertion that the disclosed K+betaM3 polypeptide has biological activities similar to known potassium channel subunits and other proteins cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological

activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the

specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Relevant literature reports that the biological functions of voltage dependent potassium channels (K_v) β subunits are not well understood (Hanlon et al. Biochem 41: 2886-2894, 2002; pg 2889, col 2, first full ¶). Roles in channel gating and cell surface expression have been the proposed functions, although these are not universal properties for all $K_v\beta$ subunits because β2

has little effect on channel inactivation while it has a role in the kinetics of activation (Hanlon et al., pg 2889, col 2, first full ¶). Furthermore, Hanlon et al. discloses that the "most notable feature of the β subunit regulation is how structurally diverse all of the β subunits are, given that they all function as modulators of structurally very similar pore-forming α subunits" (pg 2892, 4th ¶). Hanlon et al. also indicates that there is "great diversity displayed within β subunit families and the reasons behind often subtle functional variation as well as the diverse subunit combinations that are capable of assembling into functional membrane pores" (pg 2892, col 2).

It is also noted that several of the purported homologous protein sequences cited by Applicant, namely the human membrane channel protein-2, the *Drosophila* CG10465 protein, and the *Drosophila* CG10440 protein, have yet to be identified as potassium channel β subunits. For example, the *Drosophila* CG10465 protein was sequenced as part of a high-throughput process to sequence clones from Drosophila gene collections (see Genbank Accession No. AAL49143). There is no function of the protein listed. The *Drosophila* CG10440 protein is translated from a gene in the *Drosophila* euchromatic genome (see Genbank Accession No. AAF46733). There is no function of the protein listed. Furthermore, the Examiner is unable to locate the human membrane protein-2 in any database and a comparison between it and the claimed K+betaM3 polypeptide could not be made.

One skilled in the art would also not be able to recognize a variant of K+betaM3 because the specification of the instant application does not define any *specific* functional characteristics of the human K+betaM3 protein. Furthermore, one skilled in the art would not know the utility and function of K+betaM3, even if it was a putative potassium channel β subunit because, as discussed in the related art above, potassium channel subunit proteins are structurally and

functionally diverse. Therefore, the regulation and sequestration of the K+betaM3 polynucleotide and polypeptide of the instant application, are not well characterized and one skilled in the art the art would not find the utility of K+betaM3 to be obvious.

(ii) Applicant asserts that pages 24 and 29-35 of the specification disclose representative diseases that can be diagnosed, prognosed, and/or prevented that are related to the expression of the claimed K+betaM3 sequence. Applicant also argues that the antisense results of Example 6 (pg 236-244) of the specification provide evidence that the claimed sequence plays a role in the regulation and/or expression of p21. Applicant contends that modulation or expression of the claimed sequence can be used to treat disorders of the mammalian cell cycle. Applicant also submits that Example 7 of the specification (pg 244-249) demonstrates an association of the claimed sequence with the $NF_{\kappa}B$ pathway. Applicant states that based on the degree of identity/similarity between the Drosophila orthologue and the claimed K+betaM3 sequence, the claimed sequence is likely to have a function that is the modulation of one or more mammalian immune pathways.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides. In order for a polynucleotide to be useful, as asserted, for diagnosis/prognosis/prevention of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would

allow the claimed polynucleotides to be used in a diagnostic manner. Many polynucleotides are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotides are either present only in diseased tissue to the exclusion of normal tissue or are expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotides and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Furthermore, the asserted utility of regulating the expression of p21 is not specific or substantial. Such assays can be performed with any polynucleotide. The instant specification does not teach any controls or specific resulting numbers, percentages, or statistical differences. Therefore, due to little or no guidance in the specification, the skilled artisan would not conclude that K+betaM3 plays a role in the regulation and/or expression of p21. Without any specific knowledge, which could not be obtained from the instant specification, one of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Applicant's assertion that the claimed K+betaM3 polynucleotide is associated with the $NF_{\kappa}B$ pathway is not specific or substantial. Example 7 of the specification (pg 244-249) purports to correlate the function of the *Drosophila* CG10465 protein to the regulation of the *Drosophila* innate immune response. However, such assays can be performed with any

polynucleotide and Example 7 does not even utilize the claimed K+betaM3 polynucleotide. The instant specification does not teach any controls or specific resulting numbers, percentages, or statistical differences with the K+betaM3 polynucleotides. One of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner. Therefore, due to little or no guidance in the specification, the skilled artisan would not conclude that K+betaM3 is associated with the $NF_{\kappa}B$ pathway.

Appellant asserts that K+betaM3 is homologous to the Drosophila orthologue (*Drosophila* CG10465) and therefore, K+betaM3 is likely to have a function that is the modulation of one or more mammalian immune pathways. However, since the specification does not disclose any methods or working examples that demonstrate the K+betaM3 polypeptide and polynucleotide of the instant application exhibit similar activities of other beta subunit proteins, the skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a potassium channel beta subunit.

Therefore, one skilled in the art would not know the utility and function of K+betaM3 even if it was a putative potassium channel beta subunit protein because neither the prior art nor the specification provides for the physiological significance of the disclosed and proteins and polynucleotides or the purported protein homologs, the human membrane channel protein-2, the *Drosophila* CG10465, and the *Drosophila* CG10440 protein. It is also noted that according to the specification (Figure 4), K+betaM3 protein of the instant application shares a low similarity with the proposed homologs (32% similarity with Maxi-K, 38.8% similarity with *Drosophila* CG10465, and 42.6% with *Drosophila* CG10440). Although K+betaM3 is purported to share 92.5% similarity with the human membrane channel protein-2, it is noted that the Examiner is

unable to locate the human membrane protein-2 in any database and a comparison between it and the claimed K+betaM3 polypeptide could not be made. As mentioned above, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Hanlon et al. discloses that biological functions of voltage dependent potassium channels (K_v) β subunits are not well understood and the most notable feature of the β subunit regulation is how structurally diverse all of the β subunits are (pg 2889, pg 2892).

(iii) Applicant asserts that the recited utility of screening for therapeutic compounds at pg 15-16 of the Response is specific, substantial, and credible. Applicant contends that according to the Utility Guidelines, an assay method for identifying compounds that themselves have a substantial utility defines a "real world" context use (Utility Guidelines, page 6). Applicant argues that the compounds identified by the claimed method meet the substantial utility test because they are useful for treating specific disorders.

Applicant's arguments have been fully considered but are not found to be persuasive. Although Applicant contends that the K+betaM3 polynucleotide can be used in assays to screen for therapeutic compounds, this asserted utility is credible but not specific or substantial ("real world"). The various screening assays disclosed in the specification at pg 196-207 are not specific for the K+betaM3 polynucleotide and can be performed with any polynucleotide. The specification discloses nothing specific or substantial for the K+betaM3 agonists, antagonists, or other agents screened in this method. The specification does not disclose disorders associated with a mutated, deleted, or translocated K+betaM3 gene (SEQ ID NO: 1). The specification

does not disclose which disorders are associated with altered levels of the K+betaM3 gene. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

The Utility Guidelines expressly indicate that an assay method for identifying compounds that themselves have a "substantial utility" defines a "real world" context of use. However, regarding the instant application, nothing specific or substantial has been disclosed for the K+betaM3 agonists, antagonists, or other agents screened in this method. Therefore, this asserted utility is still not specific or substantial.

7. Claims 1-4, 8-9, and 16-19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pg 7 of the previous Office Action (10 June 2003).

Applicant's arguments (04 February 2004), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that the concerns for 35 USC §112, first paragraph have been addressed in the arguments made for 35 USC §101.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, since Applicant has not provided evidence to demonstrate that the K+betaM3 polynucleotide has a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Furthermore, based on

the discussions in the utility rejection, above, concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make biologically active K+betaM3 without resorting to undue experimentation to determine what the specific biological activities of the variants, domains, fragments, allelic variants, and derivatives are.

8. Furthermore, claims 1-4 and 8-9 fail to comply with the enablement requirement because the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pg 7-10 of the previous Office Action (10 September 2003).

The claims are directed to an isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95.0% identical to a sequence selected from the group consisting of: (a) a polynucleotide fragment of SEQ ID NO: 1 or a polynucleotide fragment of the cDNA sequence of ATCC Deposit No: PTA-4055, (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO: 2, (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO: 2, (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO: 2, (e) a polynucleotide encoding a polypeptide of SEQ ID NO: 2 or the cDNA sequence of ATCC Deposit No: PTA-4055, which is hybridizable to SEQ ID NO: 1, having potassium channel beta subunit activity, (f) a polynucleotide which is a variant of SEQ ID NO: 1, (g) a polynucleotide which is an allelic variant of SEQ ID NO: 1, (h) an isolated polynucleotide comprising

nucleotides 420-1097 of SEQ ID NO: 1, (i) an isolated polynucleotide comprising nucleotides 417-1097 of SEQ ID NO: 1, (j) a polynucleotide which is the complimentary sequence of SEQ ID NO: 1, (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j). The claims also recite a recombinant vector comprising the isolated nucleic acid molecule, a recombinant host cell, and a method of making an isolated polypeptide.

Applicant's arguments (04 February 2004), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that one of ordinary skill in the art, employing the guidance in the specification (such as example 14) would be able to use the invention as claimed. Applicant contends that routine experimentation is permissible and given the guidance provided in the specification and the high level of skill in the art, any experimentation a skilled artisan that might be required to practice the claimed invention would be routine and not be undue. Applicant contends that guidance is provided in the specification for performing alignments and other bioinformatics methods which can be employed to identify and/or exploit allelic variants of the claimed sequences. Applicant also argues that the specification provides a nucleic acid sequence encoding the claimed K+betaM3 polypeptide. Applicant contends that no experimentation is required, beyond the application of routine molecular biology techniques in order to use the claimed sequences to make variants and fragments useful for the purposed discussed in the specification. Applicant indicates that guidance is provided in the specification in preparing variants of the polypeptide and polynucleotides (pg 50-67, Table 3).

Applicant's arguments have been fully considered but are not found to be persuasive.

Undue experimentation would be required of the skilled artisan to generate and screen all possible K+betaM3 channel subunit proteins, variants, domains, fragments, allelic variants, and derivatives for activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such trial and error experimentation is considered undue. Additionally, undue experimentation would also be required of the skilled artisan to determine the biological activity that is associated with the claimed K+betaM3 proteins and derivatives. Although Applicant submits that the nucleic acid/protein synthesis and screening processes are routine, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one or ordinary skill in the art to determine, without undue experimentation, the positions in the K+betaM3 protein and DNA sequences which are tolerant to change and the nature and extent of changes that can be made in these positions. A specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive (MPEP § 2164.06).

Additionally, as discussed in the previous Office Action, the specification does not teach any *specific* epitopes or domains of the polypeptide encoded by SEQ ID NO: 1. Furthermore, regarding allelic variants, it is noted that such are recognized in the art as variant genes which map to the same locus on the chromosome (See Lewin, Genes II, 1985, pg 681). The specification does not disclose the chromosomal location of any of K+betaM3 gene characterized by the inventors. The specification does not teach functional or structural characteristics of any polynucleotide variants in the context of a cell or organism.

The instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Applicant and the scope of enablement set forth in the patent application. Even though Applicant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to utilizing any nucleic acid encoding a K+betaM3 potassium channel subunit protein or functionally equivalent derivative, given the lack of guidance regarding what sequences would have the desired biological activity.

(ii) Applicant asserts that the Patent Office is requiring the submission of working examples in order to comply with requirement under 35 U.S.C. § 112, first paragraph. Applicant emphasizes that the MPEP states that a U.S. patent application need not contain an example is the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation (MPEP §2164.02). Applicant cites *In re Colianni*, 195 USPQ 150 (CCPA 1977) and *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir.

1998). Applicant also argues that there is no requirement to provide examples of sequences that are at least 95% identical to SEQ ID NO: 1. Applicant submits that guidance is provided in the specification in the selection of appropriate algorithms to employ in the identification of sequences that are at least 95% identical to SEQ ID NO: 1 (pg 56-58).

Applicant's arguments have been fully considered but are not found to be persuasive. It is noted that the PTO is not requiring the submission of working examples. Although Applicant needs to not actually have reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions.

Furthermore, the fact pattern of the instant application is not inconsistent with *In re Colianni*, 195 USPQ 150 (CCPA 1977), *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Circ. 1998), or *In re Bundy* 209 USPQ 48, 51-52 (CCPA 1981). Again, although the specification in the instant application teaches art-recognized procedures for producing and screening for active

K+betaM3 polynucleotides/proteins and derivatives, this is not adequate guidance as to the nature of active K+betaM3 derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of K+betaM3 proteins and derivatives, as recited in the claims, and to screen them for a desired activity. Such trial and error is considered undue. Additionally, undue experimentation would also be required of the skilled artisan to determine the biological activity that is associated with the claimed K+betaM3 proteins and derivatives.

(iii) Applicant asserts that it is not necessary to provide information about specific epitopes or domains in order to enable the claims in view of the direction provided in the specification (pg 70-72).

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application discloses that "antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length, or longer" (pg 70, lines 15-21). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed

objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". Although the specification of the instant application teaches art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active K+betaM3 polypeptide/polynucleotide derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of polynucleotide variants and fragments of K+betaM3, as recited in the claims and to screen them for a desired activity. Such trial and error is considered undue.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed polynucleotides encoding K+betaM3, to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding same and the lack of direction/guidance presented in the specification regarding the chromosomal locus of the K+betaM3 gene disclosed in the specification, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing the unpredictability of the effects of mutation on protein structure and function, the unpredictable nature of the locus for any isolated gene, and establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to

recite particular biological activities and also embrace a broad class of structural fragments and variants and which recite any variant, allelic variant, fragment, epitope, or domain, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 1-4 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 10-13 of the previous Office Action (10 September 2003).

Applicant's arguments (04 February 2004), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

It is noted that Applicant cites pertinent case law and guidelines reviewing the legal standard of written description. The Examiner takes no issue with Applicant's general comments regarding the legal standard for written description.

(i) Applicant argues that the specification discloses an extensive list of representative species and relevant characteristics of the species, thereby satisfying the written description requirement. Applicant submits that pg 37-39 of the specification disclose an extensive list of N-terminal and C-terminal deletion polypeptides. Applicant also indicates that the specification describes the use of conservative substitutions in generating variants of the polynucleotides and polypeptides of the present invention (Table 3). Applicant states that such variants can have a different sequence from that of SEQ ID NO: 1, yet retain the properties recited in the claims.

Applicant argues that the relative level of skill in the pertinent field is very high. Applicant concludes that given the high level of skill in the field, the large number of species representative of the claimed genus, coupled with the discussion of the relevant identifying characteristics, the invention is fully described.

Applicant's arguments have been fully considered but are not found to be persuasive because the Applicant has not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polynucleotides recited in the claims. The description of one K+betaM3 polynucleotide and polypeptide in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, variants and fragments having at least 95% identity to the nucleic acid sequences of SEQ ID NO: 1. Therefore, only an isolated nucleic acid molecule consisting of the nucleotide sequence of SEQ ID NO: 1 and a nucleic acid molecule which encodes a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Furthermore, the broad brush discussion of making or screening for allelic variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only one member, K+betaM3 of SEQ ID NO: 1, is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

Furthermore, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a recitation of percent identity and polynucleotide/polypeptide fragments and variants. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

35 USC § 112, second paragraph

10. Claims 1-4 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at pg 15-16 of the previous Office Action (10 September 2003).

11. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions consisting of **A** X SSC and **B** % SDS at **C**°C"), claims 1-4 and 8-9 fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Applicant's arguments (04 February 2004), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant contends that a recitation of hybridization conditions is presented in the specification at pg 47-50, Table 2). Applicant's arguments have been fully considered but are

not found to be persuasive because it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Therefore, the claims are still rejected as being indefinite because the claims do not recite a single set of conditions as stringent.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
27 April 2004

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